DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

John A. Robinson, Ph.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Oncology
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

RE: NDA #021588
Gleevec® (imatinib mesylate) tablets for oral use
MA #457

Dear Dr. Robinson,

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed promotional materials for Gleevec® (imatinib mesylate) (Gleevec), identified as GISTexchange Case Highlights (GLI-1006264, GLI-1006367, GLI-1006265) submitted by Novartis Oncology (Novartis) under cover of Form FDA 2253. These materials are misleading because they overstate the effectiveness of Gleevec and make unsubstantiated efficacy claims for Gleevec. Therefore, your dissemination of these promotional materials misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1(e)(6)(i) and (7)(iii). These violations are concerning from a public health perspective because they suggest that Gleevec is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Gleevec.[1]

According to the FDA-approved product labeling (PI), Gleevec is indicated for, among other things, patients with Kit (CD117) positive [KIT+] unresectable and/or metastatic malignant gastrointestinal stromal tumors [GIST].

Gleevec is associated with a number of serious risks as detailed in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI. These risks include fluid retention and edema, hematologic toxicity, severe congestive heart failure and left ventricular dysfunction, hepatotoxicity, hemorrhage, gastrointestinal disorders, hypereosinophilic cardiac toxicity, dermatologic toxicities, hypothyroidism, toxicities from long-term use, fetal harm in

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

pregnant women, growth retardation in children and pre-adolescents, and tumor lysis syndrome.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Case Highlight titled "Management of a Progressive Metastatic KIT+ GIST" includes the following claims that overstate the efficacy of Gleevec:

- "Following 5 years of Gleevec therapy, disease progression was observed. . . ."
- "Six months after starting Gleevec, a [computed tomography] CT scan revealed a decrease in the size of the hepatic metastases. . . . Subsequent CT monitoring over several years showed stable disease. After 5 years on Gleevec at 400 mg/d, a restaging CT revealed progressive disease. . . ."

While these claims may be an accurate summary of this particular patient's treatment, this promotional case study misleadingly implies that Gleevec 400 mg once daily has been shown to provide all patients with metastatic KIT+ GIST with progression free survival (PFS) lasting 5 years. FDA is not aware of substantial evidence or substantial clinical experience to support this suggestion. A selected case study of one patient's treatment response does not constitute substantial evidence. As described in the PI, patients receiving Gleevec 400 mg/day in the pivotal studies experienced a median PFS of 18.9 months (95% CI 17.4-21.2). The five year duration of PFS experienced by the patient described in this Case Highlight is significantly longer than the median PFS observed in clinical trials for Gleevec in the KIT+ unresectable and/or metastatic malignant GIST patient population. We note that the Case Highlight includes a disclaimer stating, in part, "This case study was adapted from actual case files, and results are not necessarily representative and may vary by patient." However, this does not mitigate the misleading impression that patients can expect to experience PFS lasting at least five years.

The Case Highlight titled "A Patient with Unresectable KIT+ GIST" includes the following claim:

- "Progressive disease may occur in about 13% of patients with unresectable or metastatic GIST treated with Gleevec 400 mg/d.[2], [3]"

This claim misleadingly overstates the efficacy of Gleevec therapy by implying that only 13% of patients with unresectable or metastatic GIST treated with Gleevec 400 mg/day experience progressive disease, when this is not the case. The combined analysis of the two pivotal

[2] Verweij J, Casali PF, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*. 2004;364:1127-1134.
[3] Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S003. *J Clin Oncol*. 2008;26(4):626-632.

phase three clinical studies showed that 610 patients (75%) of the 818 patients with unresectable or metastatic GIST treated with Gleevec 400 mg/day progressed during this study. Therefore, the suggestion that progressive disease only occurs in 13% of patients on Gleevec therapy greatly underestimates the number of disease progression events observed in clinical trials of Gleevec in this patient population and grossly overstates the efficacy of Gleevec beyond that demonstrated by substantial evidence or substantial clinical experience.

This Case Highlight also includes the following unsubstantiated claim (emphasis added):

- "A randomized, phase 3 study reported that **approximately 1 in 3 patients** who had progressive disease while being treated with Gleevec 400 mg/d **benefited** from dose escalation to 800 mg/d.[4]"

This claim misleadingly overstates the effectiveness of Gleevec by implying a clinical benefit that has not been demonstrated by substantial evidence or substantial clinical experience. The claim makes reference to a retrospective subgroup analysis of one of the phase three studies that led to the approval of Gleevec for patients with unresectable or metastatic KIT+ GIST. The retrospective subgroup analysis reports that, of the 133 patients from this study that had progressive disease while being treated with Gleevec 400 mg once daily, three patients (2.3%) had a partial response after dose escalation to 800 mg once daily and 36 patients (27.1%) had stable disease after dose escalation. The claim that "**approximately 1 in 3 patients** who had progressive disease while being treated with Gleevec 400 mg/d **benefited** from dose escalation to 800 mg/d" is derived by combining the percentage of patients achieving a partial response and patients who had stable disease. However, in patients with GIST, stable disease is not considered to be an accurate or valid indicator of therapeutic effect due to drug therapy because stable disease may be a reflection of the natural disease process. Moreover, this retrospective subgroup analysis is insufficient to provide substantial evidence to support promotional claims pertaining to the effectiveness of Gleevec. Therefore, the implication that dose escalation of Gleevec therapy provides clinical benefit in one in three patients misleadingly implies efficacy benefits of Gleevec therapy that have not been demonstrated by substantial evidence or substantial clinical experience.

The Case Highlight titled "Differential Diagnosis and Treatment of Metastatic KIT+ GIST" makes the following claim:

- "Follow-up MRIs with and without contrast were performed 2 years after the initial diagnosis and showed that the abdomen and pelvis were completely unremarkable. . . ."

While this claim may be an accurate summary of this patient's treatment, this promotional case study overstates the efficacy of Gleevec by implying that this extremely positive result,

[4] Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer*. 2005;41(12):1751-1757.

i.e., a complete response (CR)[5] to therapy, defined as the disappearance of all target lesions, which in this case lasted for at least two years, is representative of the typical response that patients may expect from Gleevec. FDA is not aware of substantial evidence or substantial clinical experience to support this suggestion. A selected case study of one patient's treatment response does not constitute substantial evidence. In fact, we note that the Gleevec PI includes information about a phase two study of 147 patients that received Gleevec, dosed at either 400mg/day or 600 mg/day. The primary outcome measure was objective response rate (ORR), defined as CR + partial response (PR). There were 98 PRs and only one CR in the patient population. The estimated median duration of response reported for duration of ORR (CR + PR) was 118 weeks. The greater than two year duration of response in this study reflects the combined durations of CRs + PRs, and not just CR. Moreover, the single CR reported in this study lasted 11 months. These data therefore do not support the two year duration of CR implied by this presentation.

This Case Highlight also includes the following claim:

- "The patient has been on Gleevec for over 3½ years, and remains free of disease and any supervening medical problems."

While this claim may be an accurate summary of this patient's treatment experience, this promotional case study misleadingly implies that Gleevec has been shown to provide all patients with metastatic KIT+ GIST with disease free survival (DFS) lasting at least 3½ years. FDA is not aware of substantial evidence or substantial clinical experience to support this suggestion. A selected case study of one patient's treatment response does not constitute substantial evidence. DFS, defined as the time from randomization until recurrence of tumor or death from any cause,[6] was not a predefined endpoint in any of the pivotal clinical trials for Gleevec for this indication. Moreover, we are unaware of substantial evidence that demonstrates that Gleevec is effective in controlling other supervening medical problems. Once again, while we note that this Case Highlight includes a disclaimer stating in part, "This case study was adapted from actual case files, and results are not necessarily representative and may vary by patient," however, this does not mitigate the misleading nature of these claims and presentations.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Case Highlight titled "A Patient with Unresectable KIT+ GIST" makes the following unsubstantiated efficacy claim:

[5] Eisenhauer EA et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009: 45; 228-247.
[6] Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" dated May 2007.

- "Gleevec 400mg/d was given for 3 months. Following treatment, the patient's melana resolved and hemoglobin remained between 9.5 and 10.0 g/dL."

While this claim may be an accurate summary of this particular patient's treatment, it misleadingly implies that Gleevec is effective at treating melana, a symptom often present in patients with GIST, when, to our knowledge, this has not been demonstrated by substantial evidence or substantial clinical experience. The pivotal studies were not designed to evaluate the ability of Gleevec to improve disease-related symptoms such as melana.

Conclusion and Requested Action

For the reasons discussed above, these GISTexchange Case Highlights misbrand Gleevec in violation of the Act 21 U.S.C. 252(a). *Cf.* 21 CFR 202.1(e)(6)(i) and (7)(iii).

OPDP requests that Novartis immediately cease the dissemination of violative promotional materials for Gleevec such as those described above. Please submit a written response to this letter on or before January 24, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Gleevec that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Gleevec comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Adam George, Pharm.D.
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADAM N GEORGE
01/09/2012